INTERTOX

600 Stewart St.
Suite 1101
Seattle, WA 98101 Tel 206.443.2115
U.S.A. Fax 206.443.2117

March 22, 2013

David Allen, Ph.D.
Chair
US EPA Science Advisory Board
200 E Dean Keeton St. Stop C0400
Austin, TX 78712-1589

RE: Quality Review of the report *SAB Advice (02/25/13 Draft) on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate*

Dear Dr. Allen:

We appreciate the opportunity to continue our scientific dialogue with the Charter Science Advisory Board (SAB) regarding a maximum contaminant level goal (MCLG) for perchlorate. We provide these comments in the hopes that the Charter SAB will be effective, efficient, thorough, and scientifically rigorous in its review, as there are considerable data to consider and little time to review it. As we have noted before, Intertox has engaged with, conducted research, and provided scientific comments to the US EPA ("Agency") for over 10 years on behalf of the Perchlorate Study Group (PSG)[1]. We have studied the literature carefully with the goal of providing the best and most scientifically defensible science with the sole goal of protecting public health.

The document *SAB Advice (02/25/13 Draft) on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate* (Draft Report) concludes that the most sensitive population is "hypothyroxinemic pregnant and lactating women and infants exposed to perchlorate through water-based formula preparations or breast milk." Our concern with the document can be exemplified in one simple, yet critical, point regarding scientific support: the strength of the Draft Report is in its presentation of the pregnant woman and her fetus as the most sensitive population. The Draft Report presents a strong weight of evidence, evaluates data, cites a number of studies conducted in both animals and humans, compares and contrasts the literature, and provides examples that are consistent with what is understood regarding neurodevelopment and mechanism of action. This is consistent with the conclusions of other authoritative bodies such as the National Research Council (NRC), and the Agency for Toxic Substances and Disease Registry (ATSDR). In stark contrast to the presentation of the pregnant woman and fetus as most sensitive, this Draft Report provides no scientific support that the infant is also the most sensitive.

Introduction

As public health scientists, we are responsible for generating and interpreting data that can be used to protect the public from unnecessary harm. We do so using careful evaluation of the scientific database for a given chemical. The strength of the evaluation is based on the

[1] The PSG comprises Aerojet General Corporation, American Pacific Corporation, Alliant Techsystems Inc., and Lockheed Martin Corporation.

quality and, to some degree, the quantity of studies in the database. The SAB is an integral part of this process.

Compared to many environmental chemicals, the scientific database for perchlorate has studies rich in quality and quantity and spans over 60 years. While the issue brought before your committee is focused on drinking water exposures, perchlorate (e.g., potassium perchlorate[2]) has been used medically and still has some use at therapeutic levels. This provides unique human-based clinical information that is supplemented by animal and epidemiological studies.

Our first concern at the start of the SAB process was that the Agency limited the focus of review to only studies published since 2005 (please see my presentation of July 18). The concern is simple—the deliberate omission of key data would bias (from a lack of information) the evaluation the SAB was asked to consider. Additionally, the SAB was asked to review US EPA's White Paper and make its assessment in about two months (May 18 to July 18), compared to the two **year** review by the NRC in 2005. Understanding of the full database and sufficient review time would have profound impact on any expert review.

Our concern about the limited amount of review time is exemplified in this: the Draft Report states (page 13, line 2-3) there is a "…dearth of studies of perchlorate effects on neurodevelopment…" In actuality, there are at least five studies that focus on neurodevelopmental endpoints with perchlorate exposure in both humans and animals (Bekkedahl et al., 2000; Chang et al., 2003; York et al., 2004; Amitai et al. 2008; Gilbert and Sui, 2008). At least two of these studies received US EPA input, including a review of data prior to any other party. A third study was performed by US EPA scientists (Gilbert and Sui, 2008). In rats treated with doses ranging from 0.1 to 10 mg/kg-d and exposures from gestational day 0 or earlier to post-natal day 10, offspring were reported to have no effect with a range of neurobehavioral tests (Bekkedahl et al., 2000; York et al., 2004). Thus we are confused by the Draft Report's omission of these studies; they are easily obtained via a literature search, a review of authoritative documents, or through the assistance we have offered to provide.

We are further concerned about the breadth of expertise of the draft document. The draft document states that the Draft Report will "replace [as the most sensitive subpopulation] 'the fetuses of pregnant women who might have hypothyroidism or iodide deficiency' as defined by the NRC" and that hypothyroxinemia rather than hypothyroidism is the first adverse effect. The NRC included clinicians in endocrinology, pediatric endocrinology, toxicologists, and others. This type of assessment would require a full evaluation of the clinical literature and evaluation of the strengths and weaknesses of the endpoint. This was not conducted in the Draft Report.

Finally, dose-response is a key component of all chemical risk assessment evaluations. Dose response evaluation was conducted by NRC and others for perchlorate. It is absent from any evaluation of developmental (life stage) or epidemiological literature in the Draft Report.

On March 18, Intertox sent a letter to you that identified some key areas for the Charter committee to review. The four comments we identified in that letter are the following:

- The final report should not state that it supplants the NRC's determination, in its exhaustive 2005 review of the relevant perchlorate science, that the pregnant woman

[2] All salts of perchlorate dissociate in water to the metal cation and perchlorate anion, thus the active ingredient is perchlorate.

and her fetus are the most sensitive population. We note that the Panel has suggested that the hypothyroxinemic pregnant woman and her fetus, as well as the infant, are the most sensitive subpopulations.

- The final report should include a clear, thorough and complete description of how US EPA should use the Physiologically-Based Pharmacokinetic / Pharmacodynamic Model (PBPK/PD) to properly assess the potential adverse effects associated with exposure to perchlorate in drinking water at sensitive life stages.
- The final report should include a detailed evaluation of the dose-response information essential to the identification of those levels of perchlorate that produce key biological effects.
- If the infant is to be identified as the most sensitive subpopulation, the document must provide clear science-based support, with consideration of dose-response, for its discussion of the most sensitive population.

With this letter we add to our letter of March 18th and provide additional comments relevant to the questions you are asking of your lead reviewers.

We note that the scientific quality of the draft SAB report has improved from the first version, released on September 7, 2012. We believe that our comments to the SAB were useful. As we review the current draft, we still see considerable opportunity to improve the scientific rigor and content greatly.

Quality Review by the Charter SAB

During the Quality Review of the draft document *SAB Advice (02/25/13 Draft) on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate* (Draft Report), we understand the Lead Reviewers and other members of the SAB will be asked to determine whether the draft document addressed the following questions:

1. Whether the original charge questions to the SAB Standing or Ad Hoc Committees were adequately addressed.
2. Whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report.
3. Whether the Committee's report is clear and logical.
4. Whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

Intertox Response to Quality Review Questions

Since we have been involved in the process and have closely followed the development of the Draft Report, we would like to provide our assessment of whether these questions have been addressed in the Draft Report.

1. Whether the original charge questions to the SAB Standing or Ad Hoc Committees were adequately addressed.

In general, yes. The committee addresses the questions in the context of its recommendation that US EPA use a more scientific approach—the physiologically-based pharmacokinetic / pharmacodynamic (PBPK/PD) model—to derive an MCLG compared to the algebraic MCLG calculation that US EPA presented. Although the current PBPK/PD model presented by US EPA lacks transparency, in general, we support the use of a science-based PBPK/PD model to inform the risk assessment process.

We express concern that, in its charge questions, the Agency limited the ability of the SAB to investigate certain questions. For example, the Agency would have benefited greatly by asking the SAB for guidance as to how much iodide uptake inhibition (IUI) is needed to see changes in thyroid hormones in any of the sensitive population groups. The SAB should review the model presented by Lumen et al. (2013). This biologically-based dose response model presents the estimated changes in maternal and fetal thyroid hormones with exposure to varying doses of iodide and perchlorate.

The Agency also would have benefited from questioning whether the evaluation of the infant had been adequately assessed by NRC and other authoritative bodies, and if not, what data gaps should be filled in order to ensure that its evaluation is complete. To repeat, the Draft Report does an excellent job of supporting why the pregnant woman and her fetus are the most sensitive population. This support is based on studies conducted in both humans and animals. In contrast, there is not one study referenced in the current draft document that demonstrates–using the same process of citing and rigorously examining studies—why the infant is also a **most** sensitive population.

2. Whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report.

Yes. There are numerous technical errors and omissions in the Draft Report.

Technical Errors

There are different types of technical errors in the Draft Report, which are misleading to the reader. There are errors that may occur when part of a concept is presented while part is absent. For example, the Draft Report states that "Perchlorate inhibits iodide uptake and therefore interferes with thyroid hormone production." As written, this statement is incorrect as it excludes the amount of perchlorate and the frequency and duration of exposure needed to cause this effect. This is a fundamental concept in toxicology that is clearly absent from the statement. The pathway from perchlorate exposure to thyroid hormone changes is neither absolute, nor a chain reaction. Perchlorate above a threshold may begin to affect IUI, but perchlorate must be constantly increased to increase IUI, and must increase further to begin to alter thyroid hormone levels beyond homeostasis. With perchlorate's short half-life, this high exposure must occur on a daily basis and be sustained for several months. The thyroid and the body have available stores of both iodine and thyroid hormone such that IUI must be increased for several months without compensation to cause even transient changes in thyroid hormone. The NRC and ATSDR evaluated dose response particularly well and this document suffers from the lack of this assessment.

There are also errors in which data presented in published studies may not be placed in context. This is difficult to detect without familiarity with the underlying database. For example, the Draft Report states:

> Although the critical evidence is lacking to directly link perchlorate to altered brain development in humans, animal studies show that perchlorate in pregnancy is associated with compromised mammalian brain development in the progeny of perchlorate treated dams (Gilbert and Sui 2008).

This appears to provide evidence that environmental levels of perchlorate cause neurodevelopmental effects (in rats)[3]; however, critical information is not given to place this

[3] Note that the rat is not the ideal model for assessing potential human thyroidal effects from perchlorate in

study in context. The doses given in this study are much higher than environmental levels as the animals were exposed to 30, 300, or 1000 **parts per million** (ppm). As a point of reference, the No Observable Effect Level (NOEL) for perchlorate which is the point of departure (POD) for risk assessments conducted by US EPA, NRC, and ATSDR, among others, is equivalent to 245 **parts per billion** (ppb). The White Paper presented MCLG levels as low as 2 ppb. The 95th percentile of tap water samples in NHANES 2005-2006 was 1.89 ppb (Blount et al., 2010). Additionally, neurodevelopmental effects were reported in this study at the highest doses—doses that have been shown to cause overt hypothyroidism in rats.

Although not an exhaustive list, we provide additional examples in Table 1.

water as it drinks approximately five times more per body weight than a human and has lower stores of thyroid hormone making the interpretation of results more difficult than using human data.

Table 1. Examples of errors and omissions in the February 25, 2013 Draft SAB Document

Statement in SAB Draft Document (page, line)	Comment on Error	Requested Action to the Draft Document
The mode of action of perchlorate toxicity is well understood and involves the potential for disturbance of thyroid homeostasis; perchlorate limits the access of iodide to the thyroid, which in turn can lead to production of less thyroid hormone. Interference with the thyroid and available thyroid hormones is known to produce adverse effects on neurodevelopment in humans, with the fetus and infants being most vulnerable. (Letter to the Administrator, second page, line 9)	Omitted is information on dose, exposure, and magnitude of IUI or thyroid hormone reduction to cause adverse effects. Also missing is a discussion of other thyroid active chemicals such as nitrate and thiocyanate.	There is no assessment of dose response to accompany this statement. Authoritative bodies including US EPA OIG, ATSDR, and NRC have conducted this assessment. Dose response must be included throughout the document to give perspective. This is a traditional component of all risk assessments.
Thus, in the presence of perchlorate, less iodide may be available for thyroid hormone biosynthesis. (p 10, line 4-5)	The only studies in humans to cause a reduction in thyroid hormones are daily doses at therapeutic levels humans and higher exposure levels in animal studies.	This sentence needs to be amended to discuss dose as the reader will have an incorrect assessment of this parameter. This document must remove and replace these types of sentences.
Consequently, a primary downstream effect of perchlorate exposure is reduction in the levels of T3 and T4. (p 10, line 6-7)	A decrease in thyroid hormones can occur only when doses are high and exposure sustained. Importantly, the NRC estimated that IUI must be greater than 75% and sustained for several months or more. This would require a dose of at least 0.4 mg/kg-d in healthy adults.	This sentence needs to be amended to discuss dose as the reader will have an incorrect assessment of this parameter. The Draft Report must remove and replace these types of sentences.
The SAB recommends that the EPA consider sensitive life stages in developing an MCLG for perchlorate. The SAB finds that the most sensitive life stages are the fetus, neonates and	The Draft Report provides plenty of appropriate citations for the pregnant woman and her fetus as the most sensitive population. We cannot find one of similar	The Draft Report needs to either provide scientific support in a similar manner as with pregnant woman and her fetus or report to EPA that there is no scientific

infants because these are the stages when thyroid-dependent brain development occurs. (p 10, line 41-42)	quality for the infant.	support for the infant. This document must remove and replace these types of sentences or use appropriate references,
(p 10, line 26-28) Perhaps most critical, are the findings from studies examining the effects of isolated maternal 26 hypothyroxinemia, defined as a free thyroxine (fT4) value in the lower end of the normal range. This 27 research has involved a variety of cutoffs to signify maternal hypothyroxinemia ranging from fT4 below 28 the 10th or 5th percentiles to below the 2.5th percentile (Moleti et al. 2011), with the former being used to 29 investigate neurodevelopmental outcome and the latter, the incidence and effects on pregnancy (e.g., 30 Casey et al. 2005).	The Draft Report is citing studies of maternal hypothyroxinemia and use that as evidence that hypothoxinemia is the critical value to consider. Missing are studies that clinically define hypothyroxinemia. Also the merits and liabilities of using this endpoint with the one the NRC recommend is not discussed. In addition, there is no thyroid endocrinologist that was a member of the SAB panel.	The Draft Report should either scientifically support why hypothyroxinemia including with the appropriate experts or remove it from the document.
For example, evidence is available from the literature on other drug and chemical exposures showing differing absorption and metabolism rates with age and body weight (Kearns et al. 2003; Bartelink et al. 2006; Anderson and Lynn 2009). (p 10, line 26-28)	This sentence is the strongest reference to support the infant as a sensitive population. However, it is not perchlorate specific, nor do these references refer to perchlorate-like chemicals. Examination of the literature for non-metabolized chemicals similar to perchlorate demonstrates that clearance for the infant is at least similar to the adult if not greater. (See Appendix A of Intertox submittal)	The Draft Report must improve the references to demonstrate that the infant is equal to the sensitivity as the pregnant woman and her fetus. This sentence does not achieve that level of authority. This document must remove and replace these types of sentences or use appropriate references,

Omissions

The major omissions from the Draft Report include any dose-response assessment to place biological effects in context, a discussion of the effects of other chemicals that have the same mechanism of action, and how US EPA should consider the use of a non-adverse point of departure (POD).

First, dose was not assessed or considered in this draft document. Dose-response relationship is a fundamental concept in both toxicology and risk assessment, and is necessary for this assessment. The SAB document should be required to address dose-response in all aspects of its evaluation. Omission of the consideration of dose-response leads to statements in the Draft Report such as "Perchlorate inhibits iodide uptake and therefore interferes with thyroid hormone production." Based on Greer et al. (2002), perchlorate does not cause IUI until doses exceed 0.007 mg/kg-d, and transient changes in thyroid hormone were reported only with doses of 0.5 mg/kg-d. NRC (2005) has stated that "The committee notes that effects of downstream IUI by the thyroid have not been clearly demonstrated in any human population exposed to perchlorate, even at doses as high as 0.5 mg/kg per day."

Second, the contribution of other goitrogens was not considered. Nitrate and thiocyanate are both found in a normal diet in quantities that dwarf that of perchlorate. Even when considering these chemicals in perchlorate equivalence, their impact on total change in IUI is greater than 98% while that of perchlorate is less than 2%. Authoritative bodies have recommended using a cumulative risk assessment to accurately assess risk due to thyroid stressors including nitrate, thiocyanate, perchlorate, and iodine deficiency (OIG, 2010). If one were to believe that there currently exists an unmitigated public health issue due to goitrogenic compounds in food and drinking water, it is clear that deriving an MCLG for perchlorate in isolation will not provide a solution.

Third, the Agency will benefit from guidance on how to address a conservative POD that is a non-adverse effect several steps removed from the first adverse effect—possibly the first the Agency has assessed. Perchlorate is unique in that its mechanism of action and dose-response is well understood, which significantly reduces uncertainty. This provides the opportunity to develop a well-informed toxicity guideline value as opposed to the use of uncertainty factors (UFs) and other methods to deal with uncertainty. The White Paper essentially treats the NOEL for a non-adverse effect equivalent to a NOAEL for an adverse effect. This is not scientifically defensible. If NOELs were available for all environmental chemicals and this same methodology were applied, the results would profoundly alter the risk assessment paradigm.

3. Whether the Committee's report is clear and logical.

No. Given the errors and omissions in the Draft Report, this report is not as clear and logical as it must be. As noted a number of times, the Draft Report lacks data on dose response to place the information provided in the draft document into context. Without this, the reader is unable to discriminate what is relevant at what dose.

Another example where the document is not clear or logical is the lack of scientific support for the infant as equally sensitive to the pregnant woman and her fetus. If the science supports it, the document should provide this evidence; just as it clearly does regarding the pregnant woman and her fetus. If the science does not support it, then the document should state that to US EPA. It is not scientifically valid to speculate when there is a requirement to provide scientific justification.

The Draft Report does not require the Agency to provide more support on its assessment of sensitive life stages. The Draft Report does not note that the infant has been assessed by other authoritative bodies, and does not have the same level of scientific support as it provides in assessing the pregnant woman and her fetus. The draft document does not provide the Agency with information on how its current assessment of infants is inadequate. Recall that the RfD specifically addresses infants with the application of the 10-fold UF. Recent modeling has estimated that this UF is more than adequate to protect pregnant women and fetuses (Lumen et al., 2013). The NRC addressed infants specifically. No evidence is provided in the EPA White Paper[4].

The Draft Report is not clear and logical in its determination that hypothyroxinemia is determined to be a better endpoint than hypothyroidism. The listing of epidemiological studies that have used hypothyroxinemia as an endpoint does not constitute scientific support. The Agency would need to have stronger scientific justification for this conclusion. If hypothyroxinemia is a better endpoint than hypothyroidism, the Draft Report must present its investigation, evaluation, and comparison of these clinical conditions, and provide scientific support for its decision. This type of evaluation requires adequate time and expertise.

In other areas, the same opportunity exists to make a stronger document to advise the Agency. For example, the Draft Report could provide better guidance on how and when to use the PBPK model to derive an MCLG. As is, it appears that US EPA may not know how to use the PBPK/PD to derive its MCLG.

4. Whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

No. The draft document, for the many critical reason presented above, does not provide the scientific support the Agency needs.

Conclusions

In summary, we find the Draft Report that the Charter SAB is currently reviewing to be greatly improved from the first draft in September of last year. However, the document fails to provide the scientific rigor needed for the Agency to proceed. As noted above, the Agency has made a commitment to "get the science right."[5] In response, the SAB should adhere to the basic principles of the scientific method and require that the document provide the Agency with the appropriate level of scientific rigor.

This draft document should be a strong and defensible work product. To reach that level, it must:

- Correct technical errors and omissions

[4] The White Paper presents results of the PBPK/PD model that suggest that the infant may be more sensitive than other life stages. However, this model lacks transparency and contains inconsistently chosen parameters. In addition, the model reports IUI. There is no evidence to support that the most sensitive group to IUI would also be the most sensitive to an adverse effect, which would require a higher dose.

[5] Mr. Peter Grevatt told the Association of Metropolitan Water Agencies (AMWA) at its annual water policy conference in Washington, DC, March 18 that the agency is holding off on issuing its proposed maximum contaminant level goal (MCLG) for perchlorate until it has time to fully digest the final recommendations of its Science Advisory Board (SAB), which is slated to review the latest draft of its perchlorate panel's report on March 29. He said that both former EPA Administrator Lisa Jackson and current acting Administrator Bob Perciasepe have made it "very clear" to the agency's drinking water office that "our number one priority on perchlorate is to get the science right." (InsideEPA.com, 2013)

- Must be logical and clear in all aspects of the science it presents
- Must ask or challenge the Agency for its scientific rationale or support for its determination

We are not faulting the SAB Committee that generated this report. We believe the committee members are excellent scientists. We are concerned that the scope was too limited, evaluation time was insufficient, and that the breadth of expertise was too narrow to appropriately address what the Agency requested. These are all conditions that can be remedied through continued work by the Perchlorate SAB Committee, following the advice provided in this letter.

We hope you find these comments useful in your assessment of the Draft Report. We would be happy to answer questions or discuss our conclusions further.

Sincerely,

INTERTOX, INC.

Richard C. Pleus, Ph.D.
Director / Toxicologist

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